

SOME OBSERVATIONS ON MALARIA IN RELATION TO SPLENIC ENLARGE- MENT AND THE TREATMENT OF THE CRESCENTIC STAGE

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During the last two years (1908 and 1909) the city of Bombay was highly infected with malaria, the malignant tertian type being most common. This was most marked in 1908, and large numbers of cases were admitted to hospital. Several of these were in a moribund state, and the blood was found to contain typical rings and crescents in large numbers. In spite of such severe infection, it was noticed that many of them had absolutely *no fever*, and the principal sign of malarial infection, viz., *splenic enlargement*, was also absent.

The patients were in a semi-comatose stupid state, and could not be made to understand questions. In some cases parasites were found only in small numbers, and several slides had to be examined before a ring or a crescent could be detected. The crescents were looked for in several flat thick drops, which were fixed by being heated to about 70° C. for from fifteen to twenty minutes after drying them. This causes the serum to coagulate, and fix the leucocytes, blood platelets, malarial crescents and filarial embryos, if the latter are present. The haemoglobin does not coagulate at this temperature, and can be washed out by dipping the slide in distilled water. Tap water is not suitable if the Giemsa stain is to be used, as the salts in the water precipitate the stain. The slide is then stained with Giemsa's stain in the usual manner. This method is similar to the thick film one devised by Major Ross.

Various drugs were tried to study their effects on the duration of malarial crescents in the blood. It is well known that quinine has not much action on them, and this was seen to be the case in the patients under my care. In the cases under observation, although quinine was always administered in 15 grain doses at the least, there was very little reduction noticed.

Picric acid has long been recommended in malaria, but to my knowledge it is not stated what effects it is supposed to produce on these organisms. In a case of tertian malaria this acid was tried without the least benefit. Its study was taken up in cases of crescents, such of the cases as had the ring forms also present in the blood had the standard treatment with quinine; injections of the latter were also resorted to in severe cases. As control to the picric acid treatment some of the cases were treated only with quinine, either by the mouth alone or with injections as well; whilst others had quinine together with mercury perchloride, arsenic, salol and potassium iodide. The cases treated with picric acid were specially selected for the severity of infection with crescents.

18 cases had picric acid by mouth.

4 cases had injections of picrate of soda (3 c.c. daily of a 4 per cent. solution).

28 cases had quinine (with injections in six cases).

6 cases had quinine together with mercury, arsenic, etc.

The dose of picric acid was gr. 2 twice or thrice a day.

Enormous quantities of quinine (between 500 and 700 grains in different cases, as much as 915 grains having been used in one case) were administered both per os and hypodermically without any marked effect on the crescents, but on the whole under picric acid treatment the crescents seemed to disappear sooner than by any other treatment, as can be clearly seen from Table 'A.' During the time the patient is having the acid, the skin, the nails and the sclerae of the eyes show a yellow tinge as in jaundice, and the urine, too, presents a similar misleading appearance. But on adding an inorganic acid, e.g., hydrochloric or nitric acid, the colour gets paler and not deeper as in the case of urine containing bile. In Table 'A' is shown the number of days during which the crescents were found after quinine treatment alone, as compared with those

cases which had quinine and picric acid also, in the cases in which more or less complete observations were possible.

This table clearly shows that cases which received the picric acid treatment lost the crescents earlier than those which had no picric acid. The only case of picric acid treatment where the crescents continued to appear in the blood for sixty-two days was one of the most severe cases of malaria that I have seen. The patient, who was a deaf mute, was quite moribund for days together; while the analogous case without picric acid treatment from the start showed very few crescents—in fact, the ordinary smears did not show any.

The cases which lost their crescents within ten days must be regarded as cases that had probably come at the end of the crescent infection stage and thus lost them early.

Out of four cases in which crescents disappeared between ten and twenty days, three absconded, and hence they are put down as incomplete cases, while it is quite possible that the fourth case had come at the end of the crescentic infection; in fact, he was admitted for croupous pneumonia, and crescents were only found on examination of the blood as a routine method. It is not at all likely that the pneumococcic infection could produce destruction of the crescents, because the case in the simple quinine group that had crescents for sixty-two days was also suffering from the same disease at the time of admission in the hospital. In the quinine group which lost the crescents between twenty and thirty days, one case is marked incomplete for the same reason, viz., that he absconded with the crescents in the blood.

It must be borne in mind that all the cases that received the picric acid treatment were cases of specially severe infection, so that the fact that fourteen out of seventeen lost their crescents between ten and thirty days compares very favourably with the four out of seventeen of the quinine group which lost their crescents during the same period.

Again, on referring to Table 'B,' one finds that the death-rate was higher in the quinine treated cases, whether those had the spleen enlarged or not, as compared with cases which had the picric acid treatment also.

Of course the number of cases is not large, but one must bear in mind that crescent cases as a rule are not found in large numbers.

and the two years under consideration were exceptional in the fact that their number was far in excess of those I have seen in past years.

Plehn, at the British Medical Association Meeting in 1908, made the statement that the longest period that the crescents are found in the blood was six weeks; but in two of my cases they were found exactly for two months, and in one of them the last date cannot be determined, as the patient absconded from the hospital. Further, one has to consider the fact that we have no means of determining the date of the first appearance of the crescents in the blood, as all the patients were admitted in a very advanced state of the disease. Thus the total duration of the existence of these parasites must be more than two months.

Another statement by the same author concerns the diagnosis of such cases with crescents by increased urobilin in the urine. The use of an alcoholic solution of zinc acetate and Lugol's solution is described by him as the most delicate test. Both these points I was not able to confirm in my series of cases. Many of these crescents cases showed no increase of urobilin except in the very early stage, and generally at this stage the rings are still present, so that the urobilin is to be attributed rather to the blood destruction by the rings than to the presence of the crescents.

Of the two cases which showed crescents for two months, one had, from the start very few, and still they persisted for the time stated. This patient had only quinine treatment. The other had a very heavy infection, and when admitted was moribund, and so was put on picric acid treatment, but as she hardly ever swallowed her medicine, injections of picrate of soda had to be resorted to for a few days during the second month, and then the crescents soon disappeared.

The injections of picrate of soda were not found to produce any quicker results than the method of administration of picric acid by the mouth; however, in the case mentioned above it was necessary, as the patient would not take the medicines readily.

The method of preparing the solution of picrate of soda for injection is as follows:

Add 4 grams of acid picric to about 75 c.c. of boiling distilled water, and to this add, drop by drop, a strong solution of sodium hydrate, taking the reaction at the same time, with a solution of di-methyl-amido-azo-benzol till the latter no longer turns red. (Do not stop when the dimethyl turns red and subsequently fades, but go on adding the sodium hydrate solution till no change of

colour occurs.) Confirm with phenol-phthalein to see that no change of colour occurs; this latter is necessary to ascertain whether the solution has become too alkaline or not. At this stage, most of the picric acid is dissolved up. Make up the solution to 100 c.c. with distilled water; 3 c.c. of this solution is put up in test-tubes and sterilised at 120° C. in the autoclave. As the water evaporates in these tubes crystals are deposited, which can be readily dissolved either by slightly warming the tube or adding a few drops of sterile distilled water. The injections are no more painful than ordinary injections of vaccine, and do not produce any marked reaction, nor is there any nodule or swelling noticed at the site of injection. Scarcely any pain is present after 24 hours, so that there is no difficulty in injecting about 3 c.c. of this solution on consecutive days.

It will be noticed from the Table 'B' showing the percentages of recovery and death in these cases, that the percentage of death was nearly double in cases not treated with picric acid as compared with those treated with the drug. Again a very interesting point noticed in all these observations was the fact that the mortality was higher in cases where the patient had no obviously enlarged spleen. In some of these cases where a post-mortem examination was obtained, the weight of the spleen was not much above the normal, and in one case it was found quite small and tough.

Cases of benign tertian fever are generally mild, and splenic enlargement is not noticeable in most; however, in my series of twenty-seven cases of a fairly severe type of this infection three cases ended fatally, and none of them showed any splenic enlargement. In the cases of malignant tertian infection, either alone or combined with benign tertian, the mortality was very high in cases where the spleen was not found to be obviously enlarged. Thus the splenic enlargement may be looked upon as a protective response on the part of the organism to the attack of the malarial parasite; and in a case where this response does not occur, it has a tendency to end fatally. Of course in mild cases the response is also slight, but when one considers cases of moderate or extreme severity, this fact is most evident.

This appears to be a natural consequence when one considers the fact that it is the spleen that is most concerned in the destruction of these parasites. The spleen may be called the battlefield and the burial ground of the malarial parasites. Thus the splenic response is, to my mind, a very important feature for purposes of prognosis.

There were some minor points noticed in the course of the investigation which may be mentioned here. Thus one comes across cases where quinine is not absorbed at all per os, and no amount of

administration by that method is of any avail. Thus in one of my cases of mixed infection, i.e., benign tertian and malignant tertian. I found that no evidence of an alkaloid could be obtained in the urine by the picric acid and gold chloride tests, although the patient was getting fifteen to thirty grains of quinine hydrochloride daily. Together with this I found that the attacks of fever continued in spite of the quinine by the mouth. Hypodermic injections of quinine had to be resorted to, and the urine at once showed the alkaloidal test. The temperature became normal, and continued to be normal for a few days. Another attack of fever, due probably to a fresh infection, occurred, and quinine was injected with equally good result. However, I had to persist injecting it about half a dozen times and ultimately this had no effect too; the urine at that time was found to be free from quinine, thus showing that the injected quinine was not being absorbed.

The tolerance of the malarial parasite to quinine is also possible, as in some cases the patient gets an attack showing parasites in his blood, although he may be taking ten to fifteen grains of quinine daily. At this stage it is found necessary to increase the amount of the drug.

In an interesting paper on malaria by Darling* it is stated that the number of gametes diminish under quinine administration. He cites only one case, No. 48987 (*vide* Table 'C') to show that no diminution occurred when quinine was withheld. However, one must bear in mind that the patient had non-sexual forms also present in his blood at the time when these observations were made; and as quinine was withheld there is a likelihood of fresh gametes being continually formed.

If one studies the table carefully, one can see that at first there is a diminution in the number of gametes, and only in the last count a sudden increase was noticed. This shows that gametes can disappear even when no quinine is administered, and, therefore, we have up to now no evidence to show that quinine has any effect in diminishing the number of gametes. It is unfortunate that the observation was not made in Case No. 53,937, which was free from

* Annals of Trop. Medicine and Parasit., Vol. IV, No. 2, 25th July, 1910.

young asexual forms. Recently observations on these lines have been undertaken by me which will be published at a future date.

Recently a case of crescents with rings has been put on quinine gr. 30 per day till no rings could be detected. After that the quinine has been stopped, and blood smears and drops have been examined at short intervals to see whether the crescents can diminish without the administration of quinine. The annexed Table 'D' shows that there is a natural tendency for crescents to diminish even when no quinine is administered. The patient has no fever. Liver and spleen are both moderately enlarged. The patient has symptoms of dyspepsia, general debility and irritability of temper. This latter characteristic has been often noticed in crescent cases. The drops show a large and varying number of crescents, although when counted in smears one does not come across such marked differences. This shows that the counting of the smears is not a correct guide for the actual number of crescents in the blood. The diameter of each drop was between 8 and 9 mm., and the crescents were counted in these at an interval of a few days.*

TABLE A

No. of days that the crescents took to disappear from the blood when examined in drops	No. of cases treated with picric acid	No. of cases where no picric acid was given	Remarks
Less than 10 days ...	1	1	
Between 10 and 20 days ...	7	4	†3 incomplete
" 20 " 30 " ...	7	4	†1 "
" 30 " 40 " ...	1	7	1 died on 34th day
" 40 " 50 " ...	0	0	
" 50 " 60 " ...	0	0	
60 days and over ...	11	1	

* In Table D it will be noticed that the number of crescents in the drops on the first occasion was very great, and that on the third day there has been a sudden fall, which was kept up to a certain extent in subsequent counts also. Quinine administration was stopped on the 28th September, 1910, and since then none has been given. Is it likely that quinine actually retards the destruction of crescents by lowering phagocytic activity? This is a question worth considering in future observations.

† These cases absconded with crescents in their blood, and the results could not be completely ascertained.

! My notes on this case are:—Total quantity of quinine given, 915 grains. Total quantity of picric acid by mouth, 182 grains. Patients hardly ever swallowed these medicines. In spite of the quinine, rings were found in the blood a month after the commencement of treatment, this circumstance being accounted for by the drug not having been taken properly. Injections of picrate of soda were therefore commenced. Ten injections were given, one on every alternate day (in all 30 c.c. of a 4 per cent. solution, i.e., 18 grains of the acid were used during a period of 21 days from 29th December, 1909, to 19th January, 1910). Crescents disappeared in 29 days after the first injection, and they were present altogether for exactly two months.

TABLE B.—Showing the comparative mortality of Malana cases with and without splenic enlargement, and also of crescent cases under picric acid as compared with ordinary quinine treatment.

Nature of cases	Total cases	Cured	Died	Cured with splenic enlargement	Cured without splenic enlargement	Died with splenic enlargement	Died without splenic enlargement	Remarks
(No Picric) Malignant tertian with rings and crescents ...	34	25 (73.53%)	9 (26.47%)	19 (82.61%)*	4 (17.39%)*	2 (22.22%)	7 (77.78%)	• In 2 cases no record has been kept as regards splenic enlargement
(Picric Treatment) Malignant tertian with rings and crescents	22	19 (86.37%)	3 (13.63%)	10 (55.56%)†	8 (44.44%)‡	1 (33.33%)†	2 (66.67%)	† Had Picric acid for 2 days only. ‡ In 1 case no record of splenic enlargement has been kept.
Malignant tertian with rings only	38	25 (68.42%)	12 (31.58%)	17 (65.40%)	9 (34.60%)	3 (25%)	9 (75%)	
Benign tertian ...	27	24 (88.89%)	3 (11.11%)	12 (50%)	12 (50%)	0 (0%)	3 (100%)	
Malignant tertian rings plus Benign tertian ...	6	4	2	1	3	1	1	
Quartern ...	3	2	1	1	1	0	1	

TABLE C.—Case No. 48,987. Darling's Paper

1908.....	November	November	November	November	December
Date	11	24	27	30	4
Crescents ...	16	27	12	8	20

TABLE D.—Case No. 621. Shewing the natural diminution in the number of crescents without any quinine treatment.

On 21st September, 1910, rings and crescents were detected in smears; on and after 29th September, 1910, when observations were commenced, no rings could be detected.

Date	SMEAR				No. of crescents per 100 leucocytes	DROPS		
	Poly-morphs	Eosino-philic	Large hyalines	Lym-phocytes		Number of crescents in each drop 8-9 mm. diameter		
1910								
29 September	72	1	5	22	5	149	269	381
30 ..	69	0	4	27	3	—	—	—
1 October	69	2	3	26	3	18	40	65
2 ..	70	1	5	24	3	—	—	—
3 ..	58	0	5	37	3	—	—	—
4 ..	76	0	7	17	1	—	—	—
5 ..	79	3	2	26	1	—	—	—
6 ..	66	2	6	26	0	12	25	29
7 ..	65	1	4	30	0	—	—	—
9 ..	67	1	4	18	1	—	—	—
12 ..	60	3	8	29	1	2	10	0
15 ..	54	11	12	23	0	1	2	0
20 ..	62	5	7	26	0	0	0	0